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Data to Consider When Extending Practical (In-Use) Shelf Life of Drug Vials with the Tevadaptor® Closed System Transfer Device (CSTD).

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Figure 1. Tevadaptor® Vial Adaptor unit being assembled onto a glass vial.

Study Aims

The aim of the study was to test the hypothesis that Tevadaptor® CSTD can be used to extend practical shelf life of drugs by maintaining microbiological and physicochemical integrity when multiple withdrawals are made from non preserved single use drug vials.

Introduction

The preparation of potentially cytotoxic injectables is recognized as a hazardous procedure due to the potential airborne release of drug particles and vapors or droplets during manipulation (1,2). The protection of the operator undertaking the task is paramount (3). This has resulted in the development of closed system transfer devices (CSTD) designed to protect the operator undertaking hazardous drug transfers while also minimizing the risk of microbiological contamination (4). There is increasing pressure on hospital pharmacists to reduce the drug cost burden at a time of increasing healthcare costs within hospitals especially in the area of oncology. Drug costs, especially for biologicals, represents a significant part of total healthcare spending (5). One solution to this problem is drug vial optimization (DVO) through the use of a closed system transfer device (CSTD) which can form part of a storage container and help extend the practical shelf life of the drug vial after first puncture (6). Investigations to assess the ability of one commercially available CSTD device to maintain microbiological sterility up to 7 days in a non preserved drug vial have been reported (4, 7). These studies do not however report data on chemical integrity of the API, which is a prerequisite to supporting an extension of shelf life. This study reports data (8) on the use of Tevadaptor® (Figure 1) as part of the drug vial container system suitable for repeated withdrawal of hazardous drugs, demonstrating maintenance of sterility and physicochemical integrity for up to 28 days after first puncture in accordance with USP chapter <797> for Beyond Use Dating (BUD) (9).

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Maintenance of a Sterile Barrier

The ability of the Tevadaptor® system to maintain a sterile barrier was evaluated by assembling Tevadaptor® Vial Adaptor units onto 100 ml type 1 glass vials containing 50 ml sterile TSB growth medium (n=332). Aliquots (5 mL) were withdrawn from each vial on days 0, 7, 14 and 28 (n=332) by attaching a Tevadaptor® Syringe Adaptor onto the vial adaptor and then using a 5 ml sterile syringe to withdraw the growth medium. All manipulations were performed in an ISO class V environment. Each syringe was capped, incubated for 14 days at 35±1°C and then inspected for signs of microbial growth. Following withdrawal of the final sample on day 28, the vial containing the remaining growth medium (10 mL) was incubated for 14 days at 35±1°C and then examined for microbial growth. No signs of microbial growth were observed in any of the samples withdrawn during the 28 day test period or in the growth media remaining in the vial (Table 1). The growth promoting capability of the medium used in the study was verified by performing growth promotion testing (GPT) against a panel of ATCC microbiological organisms (positive controls).

Table 1. Sterility Testing of Vial and Tevadaptor® System Components During 28 Days Simulated Usage

Sample time point (n = 5)	Container type and number tested for sterility after sample withdrawal	Result (following 14 days incubation at 35±1°C)
zero	5mL Syringe (n=332)	No growth observed
7 days	5mL Syringe (n=332)	No growth observed
14 days	5mL Syringe (n=332)	No growth observed
21 days	5mL Syringe (n=332)	No growth observed
28 days	5mL Syringe (n=332)	No growth observed
28 days	Residual TSB in Type I glass drug vial (n=332)*	No growth observed
Positive Control**		Growth observed with all microbial strains

* Following withdrawal of the 28 day sample, the drug vials containing residual TSB were tested for sterility by incubating them for 14 days at 35±1°C and then examining them for microbial growth.
**Following the 14 day incubation the growth promoting capability of the media was confirmed by inoculation of sample aliquots with <100 colony forming units of 2 microbial strains and 2 fungal strains of microorganisms, as defined in the British Pharmacopoeia.

In–use Physicochemical Stability of three cytotoxic drugs

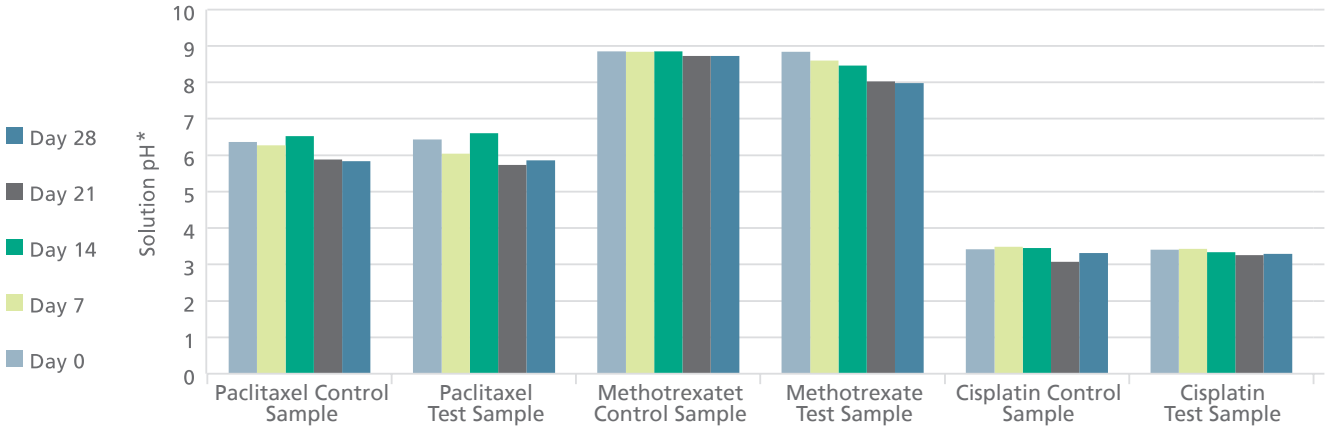
The physicochemical stability of three representative antineoplastic drugs, cisplatin (1 mg/ml solution, 100 ml vial), methotrexate (25 mg/ml solution, 40 ml vial) and paclitaxel (6 mg/ml solution, 50 ml vial), was evaluated, with the Tevadaptor® Vial Adaptor attached to the test vials, over a 28 day in-use period. Testing included measurement of the solution pH, evaluation of the HPLC diode array profile, and visual inspection for particulates and clarity. Results for test samples withdrawn from the vials containing the Tevadaptor® Vial Adaptor were compared to samples withdrawn from control vials in which the drug was withdrawn using a disposable syringe and needle (without a closed system transfer device being attached). Sample withdrawal was performed according to the instructions for use (IFU) for the Tevadator® systems and according to the drug manufacturers' instructions. A new Tevadaptor® Syringe Adaptor and disposable syringe were used for each withdrawal of samples from the vials containing the Tevadaptor® Vial Adaptor and a fresh syringe was used for each sampling from the control vials. Samples were withdrawn on days 0, 7 14, 21 and 28. Testing was performed immediately.

Solution pH

Solution pH was measured on test or control samples (n=2) using a calibrated pH meter with a standard single junction glass pH electrode. The pH meter was calibrated on the day of use and prior to measurement of samples (using NIST traceable standard solutions at pH 4.0; pH 7.0 and pH 10.0). Linearity checks were performed on the pH measurement system prior to use. The acceptance criteria for indicating drug stability was for all test solution samples to remain within ±0.5 pH unit of the appropriate control sample solution. Test results are summarized below in Figure 2. With

paclitaxel and cisplatin all of the results for the test samples were within ±0.5 pH units relative to the control samples. With the methotrexate samples, the day 0, 7 and 14 test samples were also within ±0.5 pH units of the control samples, but the day 21 and 28 test samples differed by 0.7 pH units. In both sets of the methotrexate samples (control and test samples) there is a slight negative trend in pH with increasing time. However, even with the negative trend, all of the samples were well within the 7.0-9.0 pH product specification defined in the United States and British Pharmacopoeia Monographs for Methotrexate for Injection (10, 11).

Figure 2. 28 Day In-use Stability Testing: pH



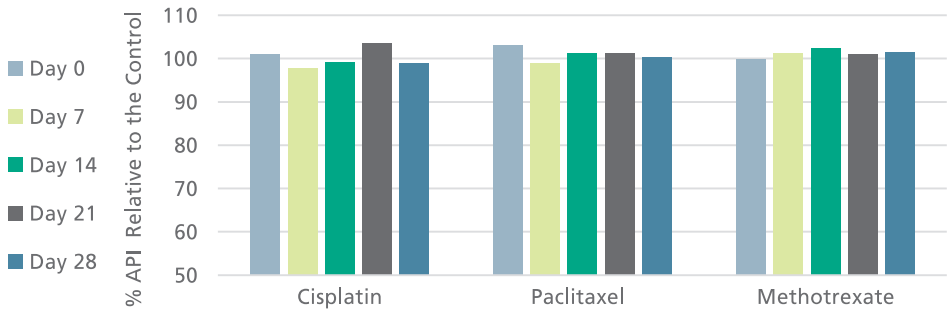
*Average of two measurements

HPLC Analysis

High Performance Liquid Chromatography (HPLC) with Diode Array detection (DAD) was utilized to evaluate the chemical integrity of drug active ingredient (active pharmaceutical ingredient-API). For each drug a stability indicating HPLC methods were developed based on a known published methods (12, 13, 14). Each of the methods was validated prior to use in the study.

Standard calibrations for instrument response and linearity were performed for each drug over an appropriate concentration range prior to the study and on each of the test time points. The study acceptance criteria was for chromatographic profile of the test sample to be qualitatively similar to that of the control sample and for the main peak area of the test sample to be within 10% of the value obtained for the control sample. Similarity of the chromatograms was established based on peak purity analysis and a match score analysis available within the Chromeleon software (v6.4) operating under windows 2000 control. The test results are summarized in Figure 3. Chromatogram profiles of the test and control samples were comparable at all time points. The percent difference between the main peak of the test samples and control samples was less than 10% for all samples tested, indicting drug product chemical stability throughout the 28 day test period.

Figure 3. Evaluation of the % API in the Tevadaptor Test Samples Relative to the Control



Bar graphs representing API content in vials with the Tevadaptor relative to control samples. Content was measured using a validated stability indicating method and was based on the area of the main peak. The acceptance criteria were for the relative difference between the main peak of the Test Sample and Control Sample to be less than 10% and for the sample chromatograms to be comparable.

Percent API Relative to Control

Sample Point	Cisplatin	Paclitaxel	Methotrexate
Day 0	100.96%	102.97%	99.92%
Day 7	97.82%	99.00%	101.11%
Day 14	99.19%	101.28%	102.48%
Day 21	103.59%	101.14%	100.95%
Day 28	98.87%	100.39%	101.39%

IRonen design

Solution Clarity, Color and Absence of Particulates

Visual inspection of two test samples and two control samples was performed to evaluate the solution for clarity, color and the presence of particulates. The visual inspection was performed against white and black backgrounds (matt) using a white fluorescent light as per the British Pharmacopoeia (15). The acceptance criteria used for stability assessment was that the solution should remain clear and free from visible particles. The cisplatin and paclitaxel solution color remained colorless and that for methotrexate maintained the same yellow color as that at the start of the study and as stated in the summary of product characteristics from the manufacturer. For all three drugs tested, no changes in solution color or clarity were observed over 28 days (Table 2). All test samples were found to be free of visible particles at the end of the study (day 28).

Table 2. Summary of Visual Inspection Results Following 28 Days In-Use Testing

Drug	Visual Inspection Results		
	Clarity	Color	Particles
Cisplatin	Clear	Colorless Solution	No particles observed
Paclitaxel	Clear	Colorless Solution	No particles observed
Methotrexate	Clear	Yellow Solution	No particles observed

Study Conclusions

In the above study we examined the in-use physicochemical stability of single use and ready to use vials of cisplatin (1 mg/mL, 100 mL), paclitaxel (6mg/mL, 50 mL) and methotrexate (25 mg/mL, 40 mL). In use stability was examined over a 28 day period with drug aliquots being withdrawn weekly. Drug stability in vials from which samples were withdrawn using a standard sterile syringe and needle approach was compared to vials that were fitted with a Tevadaptor® Vial Adaptor and samples were withdrawn using a Tevadaptor® Syringe Adaptor and sterile syringe.

In all of the physicochemical tests conducted for cisplatin and paclitaxel, the samples withdrawn using the Tevadaptor® system behaved analogously to the control samples withdrawn using a standard syringe and needle. There was no evidence for drug degradation or loss of integrity over the 28 day period following initial puncture of the drug vial. With methotrexate there were no changes in the HPLC profile or in the appearance of the Tevadaptor® samples relative to the control samples. A slight negative drift in pH was observed in both sets of samples, with a slightly higher drift in the Tevadaptor® samples relative to the control samples. All of the samples (control and Tevadaptor® samples) remained within the 7.0-9.0 pH specification defined in both the British Pharmacopoeia and United States Pharmacopoeia monograph for Methotrexate for Injection.

Sterility testing of multiple drug vials (n=332) confirmed that with all three products, sterility was maintained throughout the 28 day test period and 14 day incubation period that followed it. The sterile barrier remained intact in the drug vials fitted with the Tevadaptor® system, even when challenged with multiple withdrawals from the test vials over the 28 day test period.

With the increasing pressure on hospitals to reduce the drug cost burden, the hospital pharmacist is challenged with identifying means to reduce drug wastage, without impacting drug safety or efficacy. The data presented in this study may be used by the pharmacist to help support the decision to extend the practical in-use shelf life of drug products when used with the Tevadaptor® system.

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